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(54) Title: RELEASE–CONTROLLED COATED TABLETS

(57) Abstract

A tablet suitable for oral administration being formed from the following ingredients: a) an inner core containing a biologically active agent and conventional excipients (part B) and a pharmaceutically acceptable, water insoluble, non–swellable carrier (part A), wherein part A constitutes from 20 % to 70 % by weight of the core; b) an entering coating, which prevents gastric fluid to enter into the core thereby preventing drug release in the stomach, but being soluble in the intestinal fluid (pH > 5); and c) an outer coating consisting of one or more polymer(s), the permeability of which is independent of pH.

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Release-controlled coated tablets.

The present invention is concerned with a novel delivery system for targeting a wide variety of therapeutically active medicaments to the intestine and/or the colon. The delivery system is a tablet suitable for oral administration and comprising three parts:

a) an inner core containing a biologically active ingredient and conventional excipients,

b) an enteric coating, which prevents gastric fluid to enter into the core thereby preventing drug release in the stomach, but being soluble in the intestinal fluid (pH > 5), and

c) an outer coating consisting of one or more polymer(s). The permeability of the outer coating is independent of the pH value, therefore the release of the drug is largely unaffected by individual variations in the gastrointestinal fluids.

Among the biologically active agents which can advantageously be formulated and orally administrated in form of the tablet of the present invention, there are considered in particular active agents for which a delayed effect and/or a local effect are desired.

In a first aspect of the present invention the tablet can be used to provide controlled/delayed effect over a desired period of time.

In a further aspect of the present invention the tablet is especially suitable for time-varying delivery of a drug, the s.c. chronobiologically mode of action. E.g. patients with elevated blood pressure experience that

their blood pressure has within-day rhytmicity and that high pressure values are often seen in the morning just after the patient has woken up. Treatment of the rise in blood pressure just after awakening requires a dosage form that is administrated at bed-time and delivers the drug after a predetermined drug free period. Examples of drugs which beneficially can be delivered in this way are calcium antagonists like e.g. verapamil.

Other Examples of drugs, which are advantageously delivered in a release-controlled manner, are organic nitrates like e.g. glyceryl trinitrate or isosorbide nitrates. Especially preferred is isosorbide-5-mononitrate, (1,4:3,6-dianhydro-D-glucitol-5-mononitrate).

Isosorbide-5-mononitrate (5-ISMN) is a vasodilator and an arterial dilator. 5-ISMN is an active metabolite of 2,5-isosorbide-dinitrate, which have been used in treatment of angina pectoris for many years. Unlike the parent compound, 5-ISMN does not undergo hepatic first-pass metabolism, thus providing for a greater systemic bioavailability of the mononitrate dose. 5-ISMN is also completely absorbed from the gastrointestinal tract after oral administration and has a much longer half-life than isosorbide dinitrate. These factors make 5-ISMN a more attractive form of nitrate therapy for the management of angina and also for the development of long-acting oral nitrate forms.

It is obvious, that once-a-day dosing of a drug has advantages over twice- or three times a day dosing regimens, both from a patient compliance point of view but also because it prevents unwanted side-effects like high peak/low through plasma profile. However, if a controlled release form of 5-ISMN gives a serum con-

centration more than 100 ng/ml constantly during 24 hours, development of tolerance is likely to occur.

Nitrate tolerance may be defined as that condition where the haemodynamic responsiveness of the target tissue is lost. Whilst the direct cause of nitrate tolerance is unknown, a possibility may be changes in pharmacokinetics or to alterations in the property of target tissues such as the arterial and venal smooth muscle, making them less sensitive to the nitrate effect.

Nitrate therapy is the oldest treatment regimen for angina pectoris and the phenomenon of nitrate tolerance has been observed in humans with all commonly known nitrates, regardless of route of administration. 5-ISMN is no exception, and a need exists to design a form that overcomes this tolerance effect.

Another well-known problem to those skilled in the art of treating angina is that many angina patients chronically experience discomfort during sleep, just before awakening and for the first hour or so upon awakening. A further need exists to a form which overcomes this problem.

In US 4.956.181 to Eastman Kodak, a nitrate drug for angina pectoris is disclosed, more specifically a method and a transdermal patch for treating angina pectoris and preventing tolerance to nitrate drugs which takes into account the frequent need to provide the patient with relief or prevention of pre-waking or early morning angina. The treatment comprises administrating a daily unit dose of the nitrate before bedtime in a transdermal dosage form that provides a washout period of 3-12 hours by sufficiently retarding delivery of the nitrate from the patch to the patient during the washout period so as to provide a rate of delivery of nitrate that is so low

as to be insufficient to cause tolerance to said nitrate in said patient.

Dutch patent No. NL 155 452 to SANOL-ARZNEIMITTEL DR SCHWARZ describes release controlled tablets consisting of a granulate containing 5-ISMN, talc and sugar with controlled, linear release.

EP 163 000 B to ZERBE, H., KETTELHACK RIKER PH; 3 M MEDICA GMBH deals with controlled release pharmaceutical pellet, in which entero soluble core is coated with impermeable layer, 5-ISMN-containing depot layer and release-controlling layer.

JP 93087488 B to TOA EIYO KK concerns a sustained release preparation of hardly soluble medicine, e.g. 5-ISMN, - by pelletising mixture of 5-ISMN with release control substance and swelling high molecular weight polymer.

EP 219 161 to EURAND ITALIA describes a process for the preparation of stabilised 5-ISMN tablets, being also of sustained release, and form thus obtained. The tablets are containing PVP & hydroxypropyl methylcellulose.

In JP 62126127 to KANEBO, production of long-releasing 5-ISMN preparation by spray coating with a solution of ethylcellulose and macrogol is disclosed.

EP 240 351 to HANS LOWEY discloses a method of preparing controlled long acting pharmaceutical forms in unit dosage form having uniform and comparable bioavailability characteristics in which cellulose derivatives is mixed with 5-ISMN.

In EP 263 083 B to ROBERTO VALDUCCI, pellets with a medicament layer (e.g. 5-ISMN) applied thereon is coated with a membrane of steric acid & ethylcellulose. Sustained release from 4-22 h. is achieved.

EP 325 843 to ELAN CORP. discloses 5-ISMN oral and transdermal compositions, e.g. a once-a-day tablet. Onto non-parail seeds 5-ISMN, acid/diluent are applied and polymer blend is superimposed onto the core, which is then coated with a mix. of water-insoluble & (and to a lesser degree) water-soluble polymer, e.g. Eudragit RS® and RL®. The tablet insures a therapeutic level of ISMN in 14-18 h. followed by a wash-out period to prevent tolerance.

EP 396 425 B to KV PHARM. CO. deals with extended release oral pharmaceutical compositions containing 5-ISMN, - comprising a mixture of immediate release and coated particles for release of drug over 12-24 h. Membrane coating of the particles may be with Eudragit®.

In EP 477061, PIERRE FABRE MEDICAMENT discloses prolonged release 5-ISMN tablets - used for angina and cardiac insufficiency treatment.

The granulate comprises 5-ISMN, swelling agent, e.g. hydrophilic polymer & diluent.

WO 92/05774 to SCHWARZ PHARMA describes an orally administrated solvent free pharmaceutical preparation with delayed 5-ISMN release, in which 5-ISMN is dissolved in a matrix of polyvinylacrylate.

FREUND INDUSTRIAL CO. LDT. discloses in EP 482 576 a prolonged release dosage form of 5-ISMN and method, in which 5-ISMN is microincapsulated with a water insoluble

material, e.g. hydrophobic polymers. The microcapsules are then granulated and tabletted by conventional methods.

WO 9406414 to YAMANOUCHI concerns sustained-release preparation which releases 5-ISMN in the lower intestine for stable, sustained release, in the form of a matrix tablet consisting of 5-ISMN dissolved in hydrogel forming polymer, capable of swelling and releasing the active drug in the gastrointestinal tract.

WO 94/25010 to BYK NEDERLAND discloses a solid form of administration of 5-ISMN. An inert core with a first layer of 5-ISMN, PEG, PVP & HPMC is coated with a mixture of ethylcellulose/Eudragit 3:1 - 3:2. The release is pH independent.

WO 96/26722 to Astra discloses the use of 5-ISMN to prevent stroke in patients with isolated systolic hypertension.

In the following 2 patents, 5-ISMN is not mentioned, but technologies of relevance is described.

ROUSSEL-UCLAF describes in US 4.432.966 compressed tablets coated with two layers, the outer layer is an enterocoating persistent to acid in the stomach, the inner layer having C.R. properties.

EURAND discloses in WO 91/16042 a targeted drug release form for the small intestine or colon consisting of a plurality of multidose units (< 5 mm), having a core of drug surrounded by two membranes, i.e. an inner membrane soluble at pH >5 (e.g. Eudragit® L30D) and an outer membrane, permeable to G.I. fluids (e.g. Eudragit RS/RL). This form may be characterised by the release of no more

than 10% drug at pH lower than 5 (stomach) and 90% release at pH 6-8 in 1-1½ h. (small intestine).

Summary of the invention.

The general object of the invention is to provide a controlled release tablet, wherein the release of the biologically active agent is controlled in such a manner that the release is low, e.g. less than 10 %, in a first period of e.g. 1-6 hours and that the release is high, e.g. more than 80 %, and continuous in a second period of e.g. 3-12 hours.

This object is obtained with the tablet of the invention, the tablet being formed from the following ingredients:

a) an inner core containing a biologically active agent and conventional excipients (part B) and a pharmaceutically acceptable, water insoluble, non-swellable carrier (part A), wherein part A constitutes from 20 % to 70 % by weight of the core,

b) an enteric coating, which prevents gastric fluid to enter into the core thereby preventing drug release in the stomach, but being soluble in the intestinale fluid (pH > 5), and

c) an outer coating consisting of one or more polymer(s), the permeability of which is independent of pH.

The above-discussed release profile obtained with the tablet of the invention is believed to result from two novel factors, viz. 1) the presence of the carrier (part A) in the core and 2) the sequence of the two coatings, according to which the enteric coating constitutes the inner coating.

In one of the preferred objects of the present invention the aim is to provide angina pectoris patients with a controlled release tablet, which should be administrated at bedtime, and which tablet has a nitrate-free lag time of 1-6 hours, followed by release of 5-ISMN in a controlled manner. More particularly, the preferred object of the present invention can be described in the following way:

1) At bedtime, a tablet is administrated to a patient in need thereof, which tablet contains a premeasured amount of 5-ISMN that is effective to treat angina pectoris, which tablet has controlled release properties. During the best part of the night, no 5-ISMN is released from the tablet.

2) At a pre-determined time before awakening, release of 5-ISMN starts to prevent pre-wakening or early morning angina episodes. The release of 5-ISMN continues steadily for 3-12 hours.

3) A 5-ISMN free period follows to prevent development of tolerance.

4) At bedtime, the cycle restarts.

Detailed description of the invention.

Accordingly, the invention provides a controlled release drug containing tablet for oral administration, said tablet comprising:

a) an inner core containing a biologically active agent and a pharmaceutically acceptable carrier, which carrier

is modified in such a way that the dissolution is controlled,

b) an enteric coating, which prevents gastric fluid to enter into the core thereby preventing drug release in the stomach, but being soluble in the intestinal fluid (pH > 5),

c) an outer coating consisting of a mixture of one or more polymer(s). The permeability of the outer coating is independent of the pH value, therefore the release of the drug is largely unaffected by individual variations in the gastrointestinal fluids.

The core.

To our surprise we have found that the composition of the core is a critical factor. It has become apparent that if the core dissolutes too fast it will be impossible to produce a coated tablet with a reproducible dissolution profile. On the other hand if a core with delayed dissolution is produced, it has unexpectedly been possible to create a coated tablet with a retarded dissolution profile. This can be obtained if the carrier materials consist of two parts, A and B:

Preferably part A consists of inorganic compounds consisting of alkaline-, alkaline earth- or aluminium salts which are non-toxic and pharmaceutically acceptable, e.g. water insoluble non-swellable ingredients which can be calcium phosphate, calcium hydrogen phosphate, calcium hydrogen phosphate dihydrate, calcium carbonate, calcium sulphate, calcium silicate, calcium magnesium silicate, kaolin, magnesium oxide, magnesium carbonate, aluminium silicate, silicium dioxide or titanium dioxide. Most preferred is anhydrous calcium

hydrogen phosphate(also referred to as e.g. anhydrous dicalcium phosphate , which can be purchased from Mendell under the trade name Anhydrous Emcompress®. Anhydrous Emcompress® is a white, odourless and tasteless granular solid. It complies with the specifications of the United States Pharmacopeia (U.S.P.) and the Food Chemicals Codex (F.C.C.). Preferably, part A constitutes from 20% to 70%, preferably 40 % to 55 % by weight of the core.

Part B consists of a biologically active compound and conventional tabulating excipients, like e.g. diluents, binders and lubricants. Any conventional tablet formulating materials may be used to produce the core. The core may be prepared by any conventional means in the tablet-forming art, e.g. by direct compression or wet granulation method using a suitable tablet compression machine. Preferably, the granules are compressed into a tablet having a weight of 30-800 mg, preferably 200-800 mg and a hardness of 40-120 N.

In a preferred form, part A is anhydrous calcium hydrogen phosphate, part B is: diluent = a mixture of lactose and microcrystalline cellulose (e.g. AvicelR)), the binder = a mixture of polyethyleneglycol 6000 and polyvinylpyrrolidone (e.g. Kollidon 30), the lubricant = a mixture of talc and magnesium stearate.

The preferred dissolution profile of the core is 30-60% dissolved drug after 1 hour, 60-90% after 2 hours and > 90% after 5 hours, (according to U.S.P. 23, p. 1795-96.)

The inner coating.

The inner coating is an enteric coating which prevents penetration of gastric fluid into the core, thereby preventing any drug release in the stomach. Any

conventional enteric coating materials may be used in the delivery system of the invention.

Examples of enteric coating materials are hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate or acrylic- and/or methacrylic acid/ester copolymers. Preferred is such a copolymer which dissolves in media at and above pH 5. Most preferred is Eudragit®L30D, which is anionic in character and soluble in the intestine. The ratio of free carboxyl groups to ester groups is 1:1 and it is supplied as an aqueous dispersion containing 30% w/w dry polymer substance. Optionally, plastisizers can be added to the polymer film to enhance its characteristics.

The outer coating.

The outer coating consists of a pH independent erodible film, which is penetrated and partly solubilized in the gastrointestinal tract. This coating preferably consists of one or more polymer(s), e.g., ethylcellulose, polysiloxan or polyethylen or copolymers of acrylic- and/or methacrylic acids/esters like e.g those compounds sold under the trade name Eudragit®. Most preferred is Eudragit®RL or a mixture of Eudragit®RL and Eudragit® RS. Eudragit®RS is slightly permeable to gastric fluid, RL freely permeable. The difference between the two types is the ratio of quaternary ammonium groups to neutral acid esters, which is 1:40 for RS, 1:20 for RL. The ratio of RS to RL is the release determining factor of the outer coating, and this ratio can be from 0:100 to 100:0. Optionally, plastisizers can be added to the polymer film to enhance its characteristics. Also, dissolution modifiers can be added to the outer coating to enhance the dissolution, which excipients can be e.g. polyethylene glycol, mono-, di-, or polysaccharides like

e.g. hydroxypropylmethylcellulose, carboxy-methylcellulose, xanthan gum, lactose or sucrose.

Advantageously, a third coating can be applied to the coated tablet, a s.c. "sealcoat" which e.g. can be composed of a mixture of methylcellulose, propylene glycol and silicone liquid. The sole purpose of this sealcoat is to improve the shelf-life of the coated tablets of the invention.

If desired, a multiple unit dosage form can be prepared by filling two or more tablets according to the invention into a hard gelatine capsule.

Biologically active agents

The biologically active agents which can be incorporated into the release-controlled coated tablets are any substance which posses a therapeutic or any other beneficial action, e.g. steroids like hydrocortisone, budesonide, triamcinolone or prednisone; NSAIDS like e.g. diclofenac sodium, piroxicam, aspirin or ketoprofen; analgetic agents like e.g. codein, morphine, oxycodone or dihydromorhpone; antibiotics like e.g. amoxycillin, clavulanic acid or erythromycin, antimicrobic agents for the urogenital tract like e.g. nitrofurantoin, nalidixic acid or pipemidic acid, antihistamines and/or antiasthamatics like e.g. ephedrine, terfenadine, theophyllin or methylprednisolone; broncodilators like e.g. albuterol, salbutamol or terfenadine; antiemitics like e.g. metoclopramide; antiviral drugs like e.g. acyclovir, ribavirin or AZT; anti ulcer drugs like e.g. ranitidine or cimetidine; Anti-parkinson drugs like levodopa, carbidopa or benserazide; diuretics like e.g. furosemide or thiazides; calcium antagonists like e.g. diltiazem, nifedipine or verapamil; drugs for treatment

of hypertension like eg. ace-inhibitores (ramipril, captopril) beta-blockers (pindolol, metoprolol, sotalol) or other drugs for treatment of cardiovascular diseases like organic nitrates, e.g. nitroglycerin, isosorbide mono- or dinitrate. The active agents can be in the form of salts or derivatives, and can be administrated as a single drug or combinations of two or more drugs.

In a preferred embodiment of the invention, the active substances are drugs for treatment of various diseases associated with *pain, inflammation*, hypertension and/or heart conditions

In still another preferred embodiment the active substance is selected from ketoprofen, morphine, metoprolol and isosorbide-5-mononitrate.

Mode of action.

When a dual-coated tablet of the present invention is ingested by a patient, the tablet normally resides in the stomach for 1-2 hours. The outer coating posses the ability to swell and thereby becomes permeable for water and dissolved drugs. The permeability of the outer coating is determined by the thickness of the coating and, when the outer coating consists of a mixture of Eudragit®RS and Eudragit®RL, by the ratio of Eudragit®RS to Eudragit®RL.The outer coating begins to swell immediately after contact with liquid. When the swelling of the outer coating starts, in acidic medium, the enteric coating will prevent the core from disintegrating. After 1-6 hours, the inner coating is dissolved, and the biologically active agent will diffuse into the intestine. The prolonged release is dependent of the permeability and degradation of the coating material.

The present invention further relates to a process for preparing a tablet as defined in claim 1 comprising the steps of 1) mixing and compressing ingredients a) to form a core, 2) applying a solution/dispersion of the enteric coating b) in a first solvent onto the core and drying the coated core to remove the first solvent and 3) applying a solution/dispersion of the outer coating c) in a second solvent onto the coated core and drying the double-coated core to remove the second solvent.

In a preferred embodiment of the process of the invention, the biologically active agent is isosorbide-5-mononitrate, the core materials are anhydrous calcium hydrogen phosphate , lactose, microcrystalline cellulose, polyvinylpyrrolidone, talc and magnesium stearate, the inner coating is Eudragit®L 30 D and the outer coating is Eudragit®RL or a mixture of Eudragit®RS and Eudragit®RL.

The invention also relates to a tablet as defined in claim 1 for use as a medicament.

Furthermore, the invention relates to the use of a tablet as defined in claim 1 in the manufacture of a medicament for the treatment of angina pectoris or other heart diseases.

Finally, the invention relates to a method of treating angina pectoris or other heart diseases, wherein a tablet as defined in claim 14 is administrated to a patient in need thereof. Preferably, the tablet is administrated to the patient at bedtime to prevent pre-wakening or early morning angina pectoris.

Description of the drawings

Figures 1-5 each demonstrate the dissolution profiles of 6 tablets as a function of time. Each tablet has been measured individually. Figure 6 and 7 show the dissolution profiles of the coated tablet as a mean value of 6 tablets.

Figure 1 and Figure 3 show the dissolution of a coated tablet, in which part A of the core is absent.

Figure 2 shows the dissolution of a coated tablet, in which core a too large excess of part A has been used.

The results clearly demonstrate that the ratio between the excipients in the core of the coated tablet is a critical factor.

Figure 4 shows the dissolution of a first coated tablet according to the invention.

Figure 5 shows the dissolution of a second coated tablet according to the invention.

Figure 6 shows the dissolution of coated tablets according to the invention. Example 5 include 5-ISMN, Example 6 include metoprolol succinate and Example 7 include morphine hydrochloride. The results show that the diffusion rate of the drugs through the films depends on the physical and chemical properties of the drugs.

Figure 7 shows dissolution of coated tablets according to the invention. Example 8 include 5-ISMN, Example 9 include metoprolol succinate, Example 10 include morphine hydrochloride and Example 11 include ketoprofen.

The following, non-limiting Examples illustrate the preparation of the controlled release tablet for oral administration.

EXAMPLE 1

The core

Materials

Each tablet contains:

Isosorbide-5-mononitrate	60 mg
Lactose	189 mg
Microcrystalline Cellulose (Avicel pH 101)	30 mg
Carboxymethylcellulose sodium (Ac-Di-sol)	12 mg
Polyvinylpyrrolidon (Kollidon 30)	3 mg
Magnesium Stearate	3 mg
Talc	3 mg

Methods

The cores are being produced by wet granulation in a blade mixer. The binder solution contains 8% Kollidon 30 in ethanol/ purified water 50:50. The tablets are pressed in any tablet compression machine. The average weight of the core is 300 mg.

The inner coating

Materials

The spray suspension contains:

Methacrylic Acid copolymer (Eudragit L30D)	513.0 g
Triethylcitrate (Eudraflex)	15.4 g
Talc	93.6 g
Antifoam emulsion	2.0 g
Purified water	500.0 g

Methods

2200 g cores are being introduced into the fluidized-bed machine Glatt GPCG with the Wurster insert. The inlet-air is 34-37°C. The nozzle is placed as a bottom spray system and with a nozzle pressure of 2 atm. The product temperature is 34-35°C. The spraying rate is about 15 g/ml. The fluidized air velocity is 180-181 m^3 /hour. The cores are sprayed for a period of about 60 minutes. The tablets are finally removed from the coating machine and spread out on trays and dried at 40°C for 4 hours.

The outer coating

Materials:

The spray suspension contains:

Ammoniomethacrylate copolymer (Eudragit RL30D)	167.0 g
Ammoniomethacrylate copolymer (Eudragit RS30D)	167.0 g
Triethylcitrate (Eudraflex)	20.0 g
Talc	50.0 g
Antifoam emulsion	0.6 g
Purified water	366.0 g

Methods

The tablets are coated in the fluidized-bed machine Glatt GPCG with the Wurster insert. The inlet-air is 34-41°C. The nozzle is placed as a bottom spray system and with a nozzle pressure of 2 atm. The product temperature 33-35°C. The spraying rate is about 15 g/ml. The fluidized air velocity is 180-181 m3/hour. The cores are sprayed for a period of about 60 minutes. The tablets are finally removed from the coating machine and spread out on trays and dried at 40°C for 10 hours.

EXAMPLE 2.

The core

Materials

Each tablet contains:

Isosorbide-5-mononitrate	60 mg
Lactose	15 mg
Microcrystalline Cellulose (Avicel pH 101)	30 mg
Dibasic calciumphosphate (Emcompresss)	186 mg
Polyvinylpyrrolidon (Kollidon 30)	3 mg
Magnesium stearate	3 mg
Talc	3 mg

The cores are compressed and coated analogous with Example 1.

EXAMPLE 3.

The core

Materials

Each tablet contains:

Isosorbide-5-mononitrate	60 mg
Lactose	201 mg
Microcrystalline Cellulose (Avicel pH 101)	30 mg
Polyvinylpyrrolidon (Kollidon 30)	3 mg
Magnesium stearate	3 mg
Talc	3 mg

The cores are compressed and coated analogous with Example 1.

EXAMPLE 4.

The core.

Materials

Each tablet contains:

Isosorbide-5-mononitrate	60 mg
Lactose	15 mg
Microcrystalline Cellulose (Avicel pH 101)	75 mg
Polyethylene glycol 6000	6 mg
Calcium hydrogen phosphate dihydrate (Calstar)	135 mg
Polyvinylpyrrolidon (Kollidon 30)	3 mg
Magnesium stearate	3 mg
Talc	3 mg

The cores are compressed and coated analogous with Example 1.

EXAMPLE 5

The core composition and the inner coating are analogous with Example 4.

The outer coating

Materials:

The spray suspension contains:

Ammoniomethacrylate copolymer (Eudragit RL30D)	251.00 g
Ammoniomethacrylate copolymer (Eudragit RS30D)	84.00 g
Triethylcitrate (Eudraflex)	20.00 g
Talc	50.00 g
Antifoam emulsion	0.55 g
Purified water	403.00 g

Methods

The tablets are coated in the fluidized-bed machine Glatt GPCG with the Wurster insert, analogous with the outer coating in Example 1.

EXAMPLE 6

The core composition is analogous with Example 4, but 5-ISMN is substituted with metoprolol succinate. The inner coating is analogous with Example 4, and the outer coating is analogous with Example 5.

EXAMPLE 7

The core composition is analogous with Example 4, but 5-ISMN is substituted with morphine hydrochloride. The inner coating is analogous with Example 4, and the outer coating is analogous with Example 5.

EXAMPLE 8

The core

Materials

Each tablet contains:

Isosorbide-5-mononitrate	60 mg
Lactose	26 mg
Microcrystalline Cellulose (Avicel pH 101)	75 mg
Polyethylene glycol 6000	6 mg
Anhydrous calcium hydrogen phosphate (Emcompress, anhydrous)	124 mg
Polyvinylpyrrolidon (Kollidon 30)	3 mg

The inner coating.

Materials

The spray suspension contains:

Methacrylic Acid copolymer (Eudragit L30D)	333,00 g
Triethylcitrate (Eudraflex)	10,00 g
Talc	51,00 g
Antifoam emulsion	1,25 g
Purified water	294,00 g

The outer coating

Materials:

The spray suspension contains:

Ammoniomethacrylate copolymer (Eudragit RL30D)	200,0 g
Triethylcitrate (Eudraflex)	12,0 g
Talc	30,0 g
Antifoam emulsion	0.3 g
Purified water	219,0 g

The cores are compressed and coated analogues with Example 1.

EXAMPLE 9

The core composition is analogous with Example 4, but 5-ISMN is substituted with metoprolol succinate. The two coatings are analogous with Example 8.

EXAMPLE 10

The core composition is analogous with Example 4, but 5-ISMN is substituted with morphine hydrochloride. The two coatings are analogous with Example 8.

EXAMPLE 11

The core composition is analogous with Example 4, but 5-ISMN is substituted with ketoprofen. The two coatings are analogous with Example 8.

Dissolution of 5-ISMN from the core (% of total)								
Ex.	Friability %	Crushing strenght N	30 min.	1 hour	2 hours	3 hours	4 hours	6 hours
1	0,2	55	106					
2	0,6	52	100	101				
3	0,2	100	87	104				
4	0,4	83	37	51	71	86	96	106

Dissolution test

Dissolution of the 5-ISMN core, according to USP 23 p.1795-1796. Dissolution was performed by means of the basket method, the medium consisted of 0,02M tribasic phosphate solution. The samples were analysed using Shimadzu UV-spectrophotometer 220 nm.

Dissolution of 5-ISMN coated tablet according to USP 23 p.1795-1796. After 2 hours of operation in 0,1N hydrochloric acid, the pH was adjusted to 6,8 pH with 0,02M tribasic phosphate. The samples were analysed using Shimadzu UV-spectrophotometer 220nm, or HPLC; mobile phase methanol/ water 25:75, flow 0,8 ml/min, detection 230 nm by Shimadzu UV-spectrophotometer.

The samples from Examples 1 + 5 were analysed using HPLC and the samples from Examples 2+3+4 were analysed using UV at 220 nm.

The coated tablets from Examples 7+10 were analysed using Shimadzu UV-spectrophotometer at 285 nm, the coated tablets from Examples 6+9 were analysed using Shimadzu UV-spectrophotometer at 274 nm, and the coated tablets from Example 11 were analysed using Shimadzu UV-spectrophotometer at 258nm. The values of the UV-analysis of Examples 6+7+9+10+11 were corrected for the absorbents of a placebo tablet.

CLAIMS:

1. A tablet suitable for oral administration being formed from the following ingredients:

a) an inner core containing a biologically active agent and conventional excipients (part B) and a pharmaceutically acceptable, water insoluble, non-swellable carrier (part A), wherein part A constitutes from 20 % to 70 % by weight of the core,

b) an enteric coating, which prevents gastric fluid to enter into the core thereby preventing drug release in the stomach, but being soluble in the intestinale fluid (pH > 5), and

c) an outer coating consisting of one or more polymer(s), the permeability of which is independent of pH.

2. A tablet according to claim 1, in which the water insoluble, non-swellable ingredient(s) of the core is/are selected from inorganic compounds.

3. A tablet according to claim 2, wherein the inorganic compound of the core is selected from alkaline-, alkaline earth- or aluminium salts, TiO_2 or SiO_2.

4. A tablet according to claim 3, wherein the inorganic compound of the core is selected from calcium phosphate, calcium hydrogen phosphate, calcium sulphate, calcium carbonate, calcium silicate, calcium magnesium silicate, kaolin, magnesium oxide, magnesium carbonate or aluminium silicate or mixtures thereof.

5. A tablet according to claim 4, wherein the inorganic compound of the core is anhydrous calcium hydrogen phosphate.

6. A tablet according to any of the claims 1-5, in which the dissolution of the core, according to U.S.P. 23, p. 1795-96, releases no more than 60 % of the biologically active agent within the first 30 minutes and at least 90% after 3-9 hours.

7. A tablet according to any of claims 1-6, wherein the enteric coating consists of a coating material selected from hydroxy propyl methyl cellulose phthalate, polyvinyl acetate phthalate, copolymers of acrylic- and/or methacrylic acid/esters or mixtures thereof.

8. A tablet according to claim 7 in which the enteric coating consists of copolymers of acrylic- and/or methacrylic acid/esters known as Eudragit® L30D .

9. A tablet according to any of the claims 1-8 wherein the outer coating is selected from one or more polymer(s) which can be ethylcellulose, polysiloxan, polyethylene or copolymers of acrylic- and/or methacrylic acids/esters.

10. A tablet according to claim 9 wherein the outer coating is selected from copolymers of acrylic- and/or methacrylic acids/esters known as Eudragit®RL, Eudragit ®RS or mixtures thereof.

11. A tablet according to any of the claims 1-10 wherein dissolution modifiers are present in the outer coating.

12. A tablet according to claim 11 wherein the dissolution modifiers are selected from polyethylen

glycol, hydroxy methylpropylcellulose, carboxy-methylcellulose, xanthan gum, lactose or sucrose.

13. A tablet according to any of the claims 1-12 wherein the core consists of a biologically active agent, anhydrous calcium hydrogen phosphate, lactose, microcrystalline cellulose, polyvinylpyrrolidone, talc and magnesium stearate.

14. A tablet according to any of the preceding claims, wherein the biologically active agent is selected from morphine, ketoprofen, metoprolol and isosorbide-5-mononitrate.

15. A tablet according to any of the preceding claims, wherein the tablet has a lag time of 1-6 hours (release of biologically active agent < 10 %), followed by release of biologically active agent for 3-12 hours (release > 80 %).

16. A process for the preparation of a tablet according to any of the claims 1-15 comprising the steps of 1) mixing and compressing ingredients a) to form a core, 2) applying a solution/dispersion of the enteric coating b) in a first solvent onto the core and drying the coated core to remove the first solvent and 3) applying a solution/dispersion of the outer coating c) in a second solvent onto the coated core and drying the double-coated core to remove the second solvent.

17. A process according to claim 16, in which the biologically active agent is morphine, ketoprofen, metoprolol or isosorbide-5-mononitrate, the core materials are anhydrous calcium hydrogen phosphate, lactose, microcrystalline cellulose, polyvinyl-pyrrolidone, polyethylene glycol, talc and magnesium

stearate, the inner coating is Eudragit®L 30 D and the outer coating consists of Eudragit® RL.

18. A process according to claim 16, in which the biologically active agent is morphine, ketoprofen, metoprolol or isosorbide-5-mononitrate, the core materials are anhydrous calcium hydrogen phosphate, lactose, microcrystalline cellulose, polyvinyl-pyrrolidone, polyethylene glycol, talc and magnesium stearate, the inner coating is Eudragit®L 30 D and the outer coating is a mixture of Eudragit® RS and Eudragit® RL.

19. A tablet according to any of the claims 1-15 for use as a medicament.

20. Use of a tablet according to any of the claims 1-15 in the manufacture of a medicament for the treatment of pain, inflammation, hypertension, angina pectoris or other heart diseases.

21. A method of treatment of angina pectoris or other heart diseases wherein a tablet according to claim 14 is administrated to a patient in need thereof.

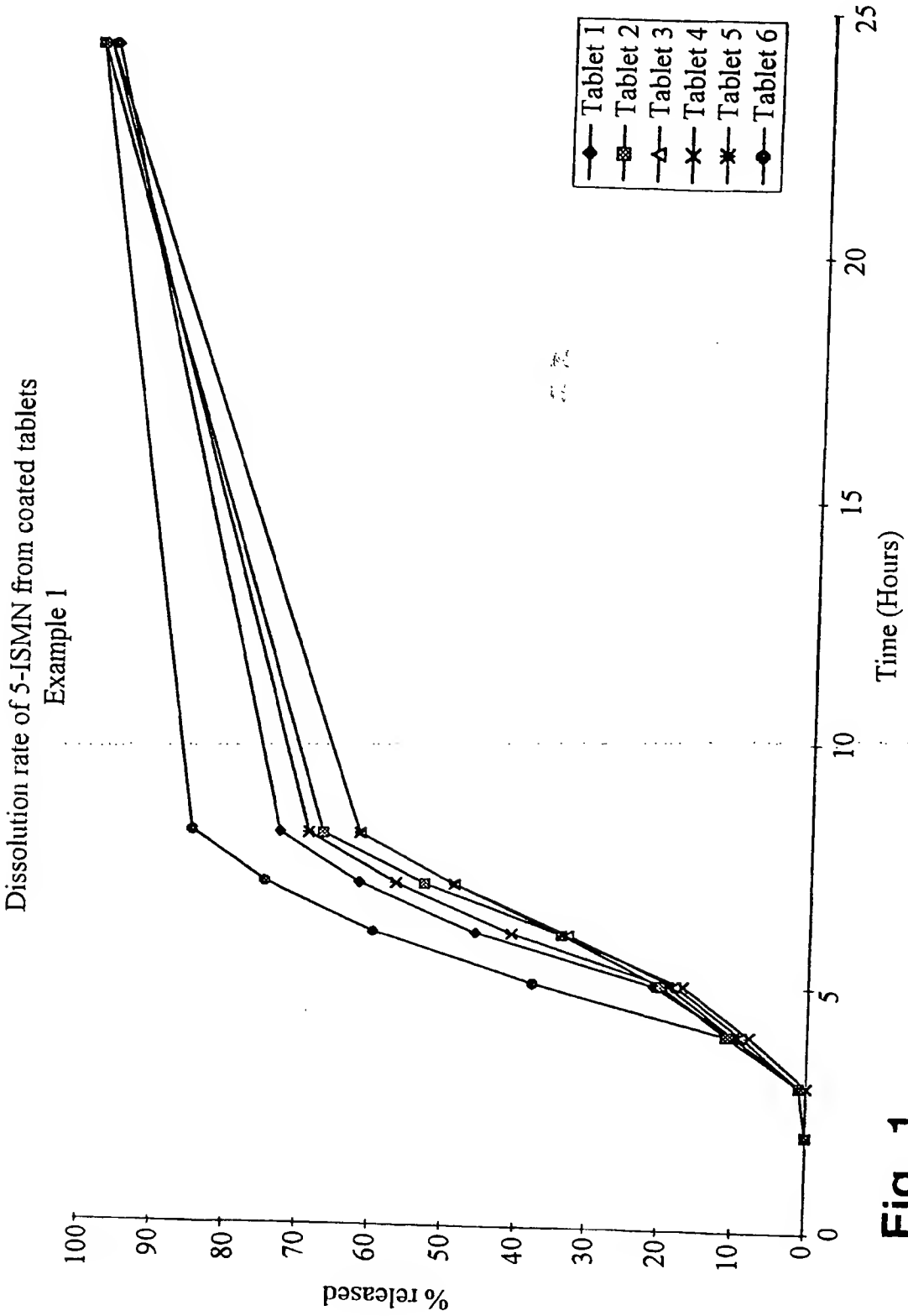
Dissolution rate of 5-ISMN from coated tablets
Example 1
% released
Time (Hours)
Tablet 1
Tablet 2
Tablet 3
Tablet 4
Tablet 5
Tablet 6
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25

Fig. 1

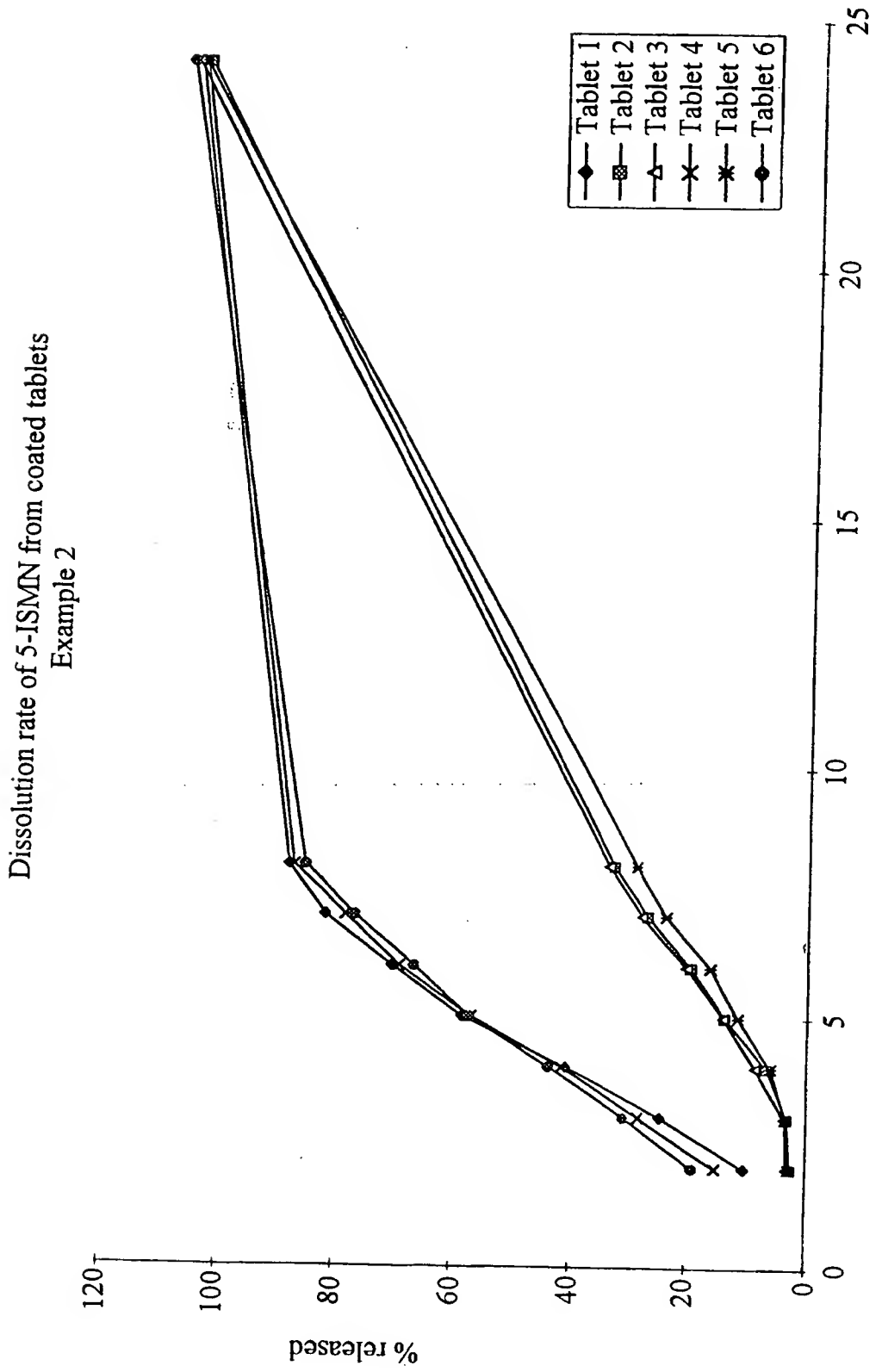
Dissolution rate of 5-ISMN from coated tablets
Example 2
Tablet 1
Tablet 2
Tablet 3
Tablet 4
Tablet 5
Tablet 6
% released
Time (Hours)
0
20
40
60
80
100
120
0
5
10
15
20
25

Fig. 2

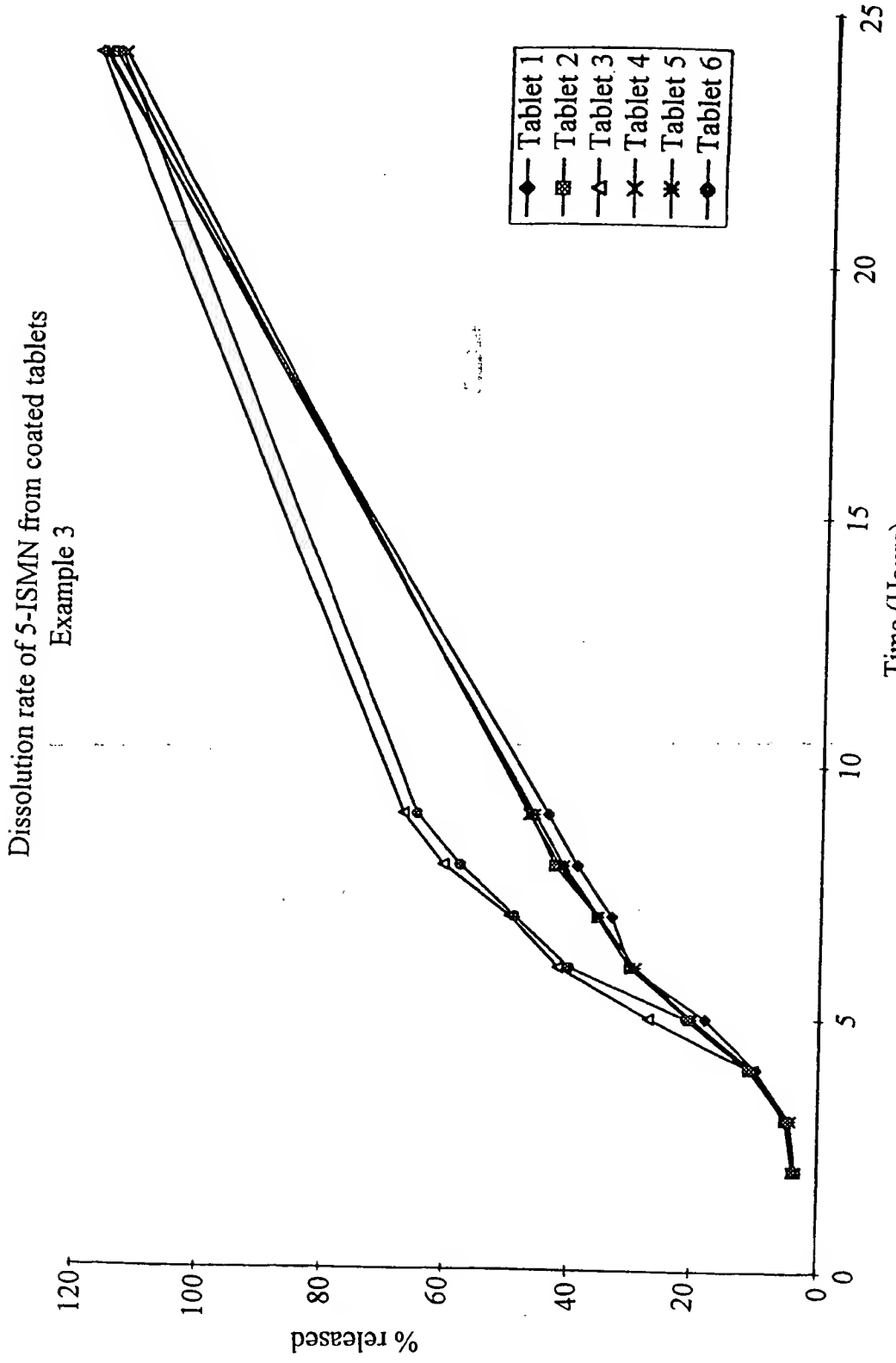
Dissolution rate of 5-ISMN from coated tablets
Example 3
Tablet 1
Tablet 2
Tablet 3
Tablet 4
Tablet 5
Tablet 6
% released
Time (Hours)
0
20
40
60
80
100
120
0
5
10
15
20
25

Fig. 3

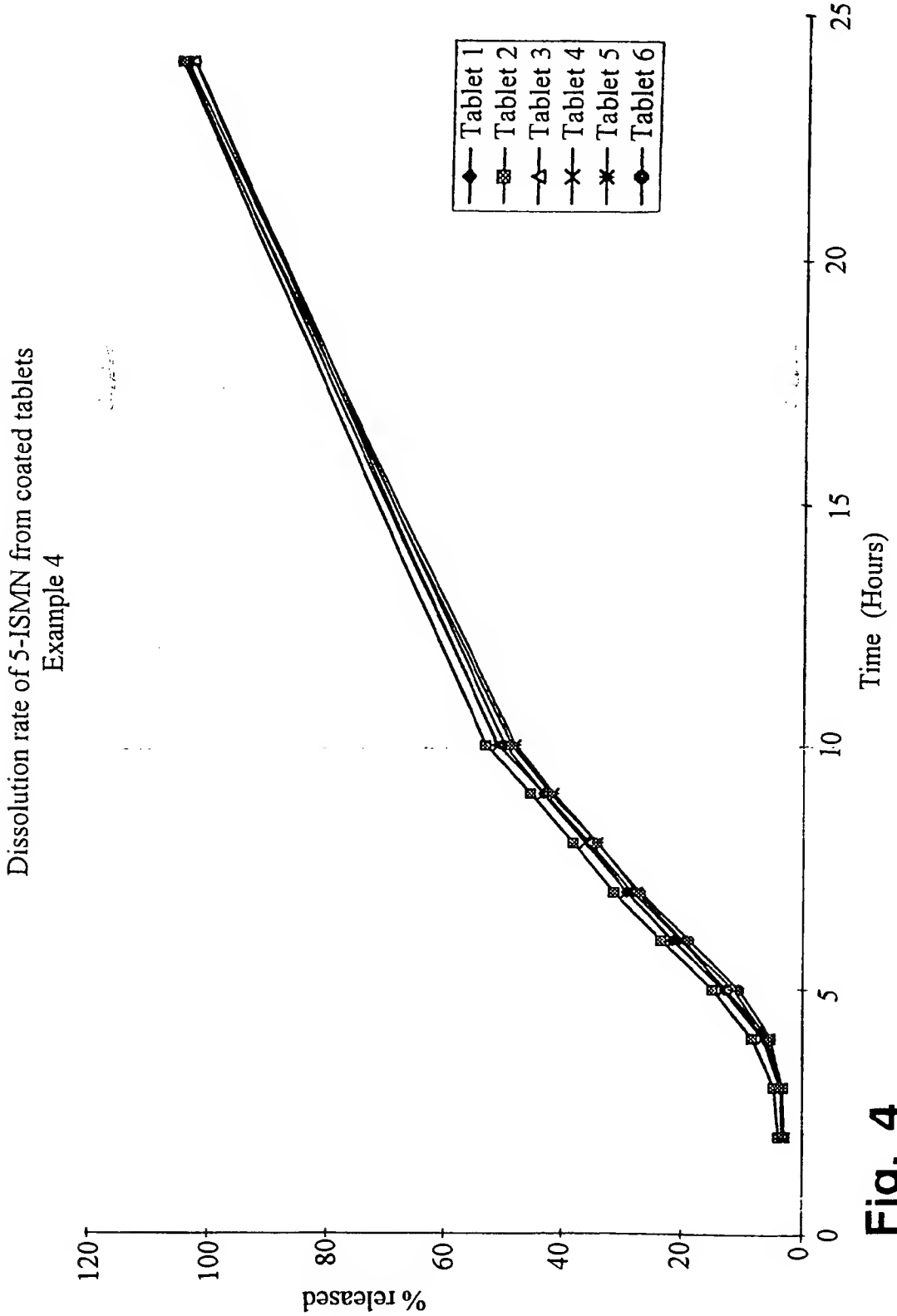
Dissolution rate of 5-ISMN from coated tablets
Example 4
Tablet 1
Tablet 2
Tablet 3
Tablet 4
Tablet 5
Tablet 6
% released
Time (Hours)
0
20
40
60
80
100
120
0
5
10
15
20
25

Fig. 4

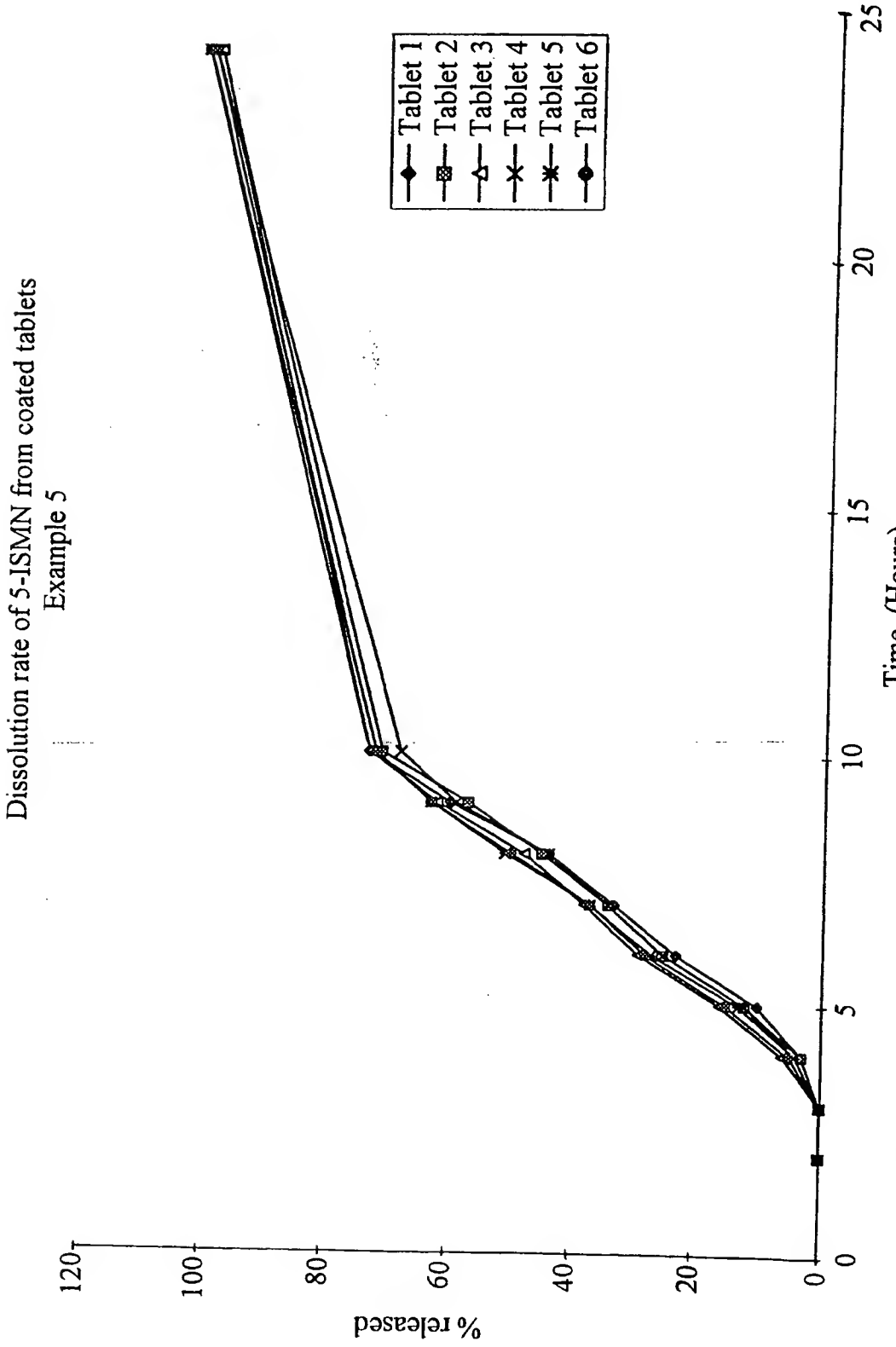
Dissolution rate of 5-ISMN from coated tablets
Example 5
Tablet 1
Tablet 2
Tablet 3
Tablet 4
Tablet 5
Tablet 6
% released
Time (Hours)
0
20
40
60
80
100
120
0
5
10
15
20
25

Fig. 5

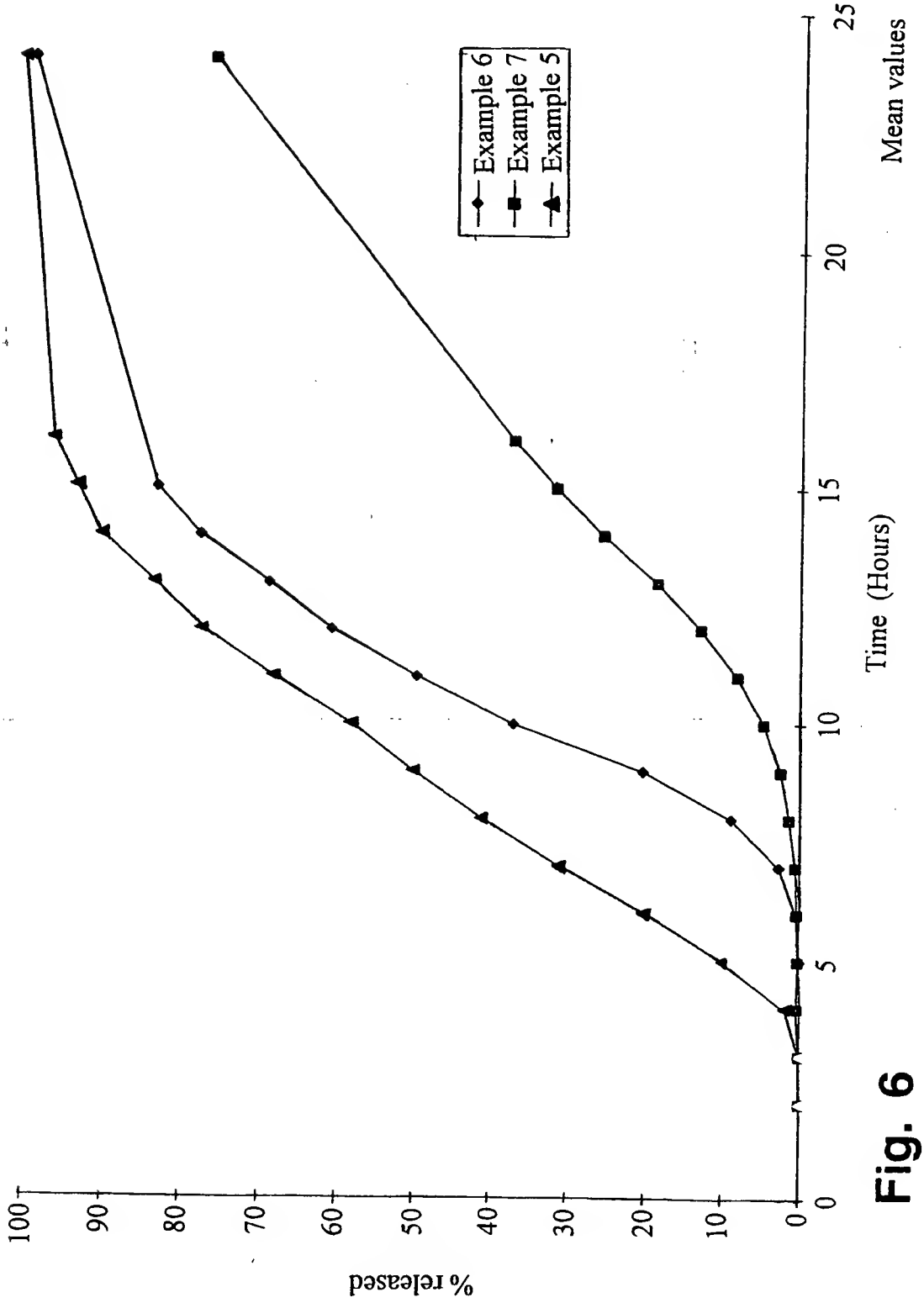
Example 6
Example 7
Example 5
Mean values
Time (Hours)
% released
0
5
10
15
20
25
10
20
30
40
50
60
70
80
90
100

Fig. 6

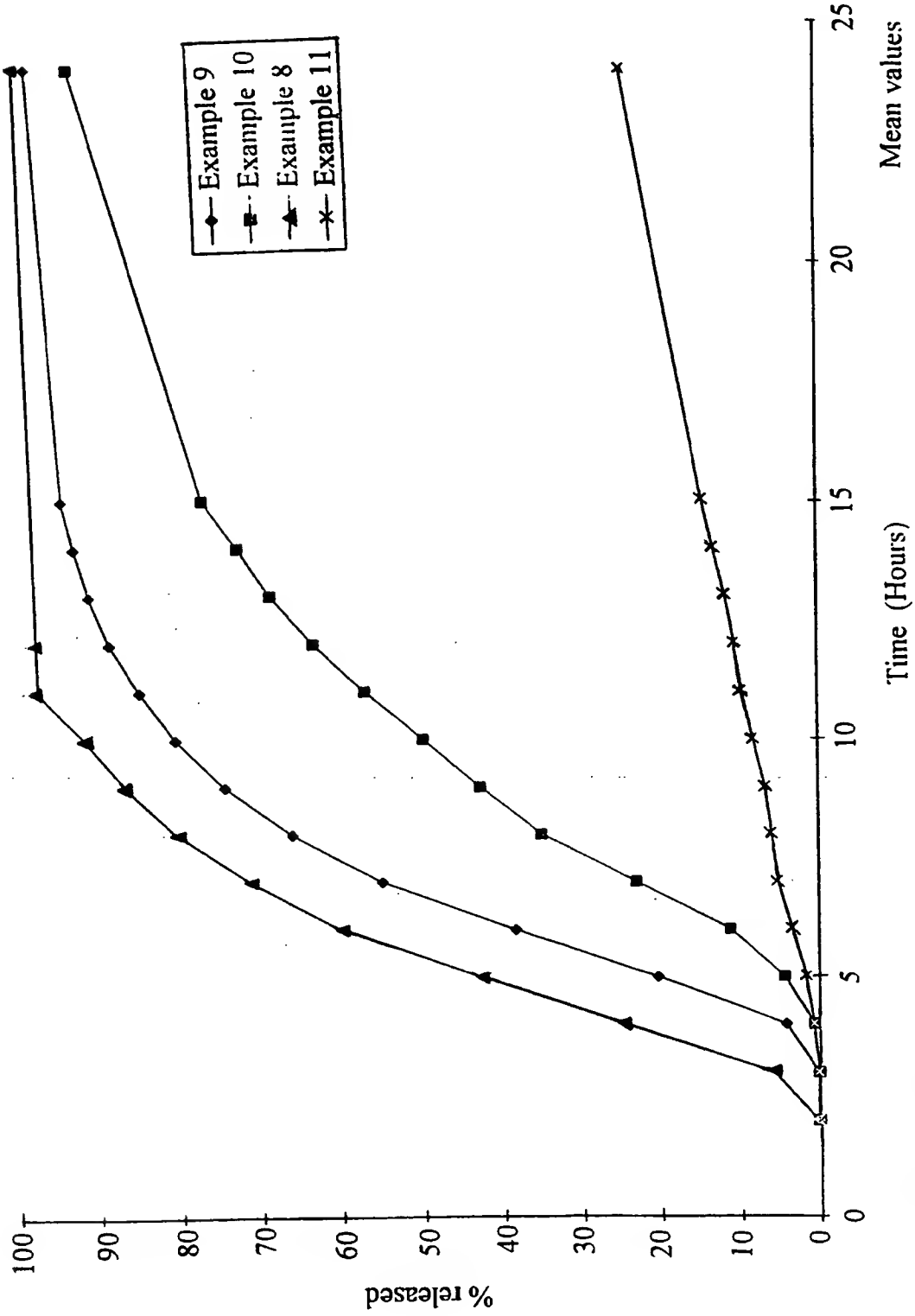
Example 9
Example 10
Example 8
Example 11
% released
Time (Hours)
Mean values
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00582

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/28, A61K 9/50, A61K 31/34, A61K 31/485, A61K 31/635, A61K 31/13
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, USPATFULL, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0277925 A1 (LEJUS MEDICAL AKTIEBOLAG), 10 August 1988 (10.08.88) --	1-21
X	WO 9116042 A1 (EURAND INTERNATIONAL SPA), 31 October 1991 (31.10.91), page 5, line 7 - page 8, line 26, claims --	1-21
X	US 4432966 A (PAUL ZEITOUN ET AL), 21 February 1984 (21.02.84), column 2, line 6 - column 4, line 5, claims --	1-21
X	EP 0163000 A2 (KETTELHACK RIKER PHARMA GMBH), 4 December 1985 (04.12.85) --	1-21

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1998	20 -04- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00582

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9626722 A1 (ASTRA AKTIEBOLAG), 6 Sept 1996 (06.09.96) --	1-21
A	WO 9425010 A1 (BYK NEDERLAND BV), 10 November 1994 (10.11.94) --	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00582

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 21 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/04/98

International application No.
PCT/DK 97/00582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		ES 2093097 T	16/12/96
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